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THE IMPACT OF LONG TERM OPIOID MEDICATION ON ORAL ANTIHYPERGLYCMIC MEDICATION ADHERENCE AND SUBSEQUENT TYPE 2 DIABETES MELLITUS RELATED HOSPITALIZATION RISK AMONG INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS: A RETROSPECTIVE DATABASE ANALYSIS

by

Nipun Atreja, MS

A dissertation submitted in partial fulfillment of

the requirement for the degree of

DOCTOR OF PHILOSOPHY

IN

PHARMACEUTICAL HEALTH OUTCOMES AND POLICY

University of Houston

College of Pharmacy

____ 2016

THE IMPACT OF LONG TERM OPIOID MEDICATION ON ORAL ANTIHYPERGLYCMIC MEDICATION ADHERENCE AND SUBSEQUEENT TYPE 2 DIABETES MELLITUS RELATED HOSPITALIZATION RISK AMONG INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS: A RETROSPECTIVE DATABASE ANALYSIS

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my academic advisor Dr. Marc L. Fleming for his guidance, trust, encouragement, and all the help during my entire duration of the doctorate program. His guidance helped me during my research and writing of the dissertation. I could not have imagined having a better advisor and mentor for my doctorate program.

I would also like to express my heartfelt appreciation for Dr. Michael L. Johnson and Dr. Hua Chen for their kind assistance, inputs, and guidance during my entire doctorate program and dissertation research. I would also like to thank Dr. Natalia Zhivan and Dr. Knox H. Todd for helping me with the study design and study's research objectives.

I am also thankful to the Truven MarketScan® for providing me with the study data for my dissertation research.

I owe a special thanks to Dr. Rajender Aparasu for his support during my graduate studies. I would like to thank my friends specially Ms. Nandita Kachru, Ms. Aisha Vadhariya and Mr. Navneet Upadhyay for their support.

Finally, I would like to thank my family who have always supported me and guided me at every stage of my life.

Dedicated to

Family

&

Friends

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CHAPTER ONE: INTRODUCTION

1. 1 Background

Diabetes mellitus has been defined as a condition characterized by hyperglycemia resulting from defects in insulin secretion from the pancreas or the body's inability to use insulin correctly (American Diabetes Association, 2009). The most common form of diabetes is type 2 diabetes mellitus (T2DM) which is typically associated with insulin resistance. T2DM affects approximately 90% to 95% of patients diagnosed with diabetes (Olokoba, Obateru, & Olokoba, 2012).

Among patients with T2DM, adherence to antihyperglycemic medication is a major contributor to achieving adequate glycemic control (Lau & Nau, 2004). Pharmacotherapy for T2DM management (e.g., sulfonylureas, biguanides) can play a vital role in controlling symptoms and preventing complications, but non-adherence of antihyperglycemic medications is highly prevalent (Blackburn, Swidrovich, & Lemstra, 2013). Non-adherence of antihyperglycemic medications has been linked to increases in morbidity, mortality, and health care costs (Bagonza, Rutebemberwa, & Bazeyo, 2015). Non-adherence can also lead to micro vascular and macro vascular complications (Cziraky et al., 2015).

Opioid analgesics are a class of medication used for the management of pain and cough. Some of the most common prescription opioids used for the management of pain are oxycodone, hydrocodone, and morphine (National Institue of Health, 2016). Prescription opioids are also approved to treat cough (e.g., codeine) (Chung, 2005). Opioids produce analgesia by preventing the pain causing neurotransmitter release from the primary afferent terminals in the spinal cord, thus preventing the activation of inhibitory controls in the midbrain (Smith H.S., 2009).

Pain is associated with increased action in primary sensory neurons caused by an internal stimuli in the body (Dubin & Patapoutian, 2010). Chronic pain is a prevalent condition that impacts a patient's daily activity and has a significant impact on the healthcare system (Butchart, Kerr, Heisler, Piette, & Krein, 2009). Chronic pain is often defined as any pain lasting more than 12 weeks (e.g., low back pain, arthritis pain) (MedlinePlus, 2011). Approximately one-third of adults have chronic or acute pain and the prevalence of chronic pain increases with age (Volkow & McLellan, 2016). Additionally, 40% of the elderly suffer from chronic pain (Volkow & McLellan, 2016). Chronic pain has also been linked to reduced quality of life, increased medical expenditures, and loss of employment (Butchart et al., 2009).

Patients with T2DM often have chronic pain due to other therapeutic conditions. Due to the high prevalence of chronic pain, prescription opioids are now the most commonly prescribed medications in the United States (Volkow & McLellan, 2016). Although, prescription opioids relieve pain, they have associated side effects when prescribed over long durations of time (e.g., over 3 months) (Berland & Rodgers, 2012; Volkow & McLellan, 2016). Prescription opioids are habit forming and their long-term use is linked with negative effects (Dr. Donald Teater, 2016). Furthermore, a lack of evidence supporting the long-term use of prescription opioids for pain management raises concern about the safety of these medications in T2DM patients (Noble et al., 2010). According to the Substance Abuse and Mental Health Services Administration (SAMHSA) guidelines on chronic pain management, prescription opioid users are likely to fail to adhere to their other chronic treatment regimens and are at greater risk for aberrant drug related behavior (ADRB) (Substance Abuse and Mental Health Services Administration, 2012). ADRBs are characterized by behavior that suggests controlled substance prescription overuse, addiction or abuse. Further, patients exhibiting ADRBs including actions such as falsification of prescriptions,

obtaining medications from non-medical sources, demanding more medication than prescribed, and resisting drug testing. Patients that demonstrate ADRBs can often become more interested in prescription opioids, as opposed to other medications (e.g., hypertension therapy) or in any other aspect of treatment. Therefore, patients with T2DM who are also prescribed prescription opioids may be at greater risk for poorer health outcomes associated with non-adherence of antihyperglycemic medications.

1.2 Statement of Purpose

The aims of this study are to understand the effect of prescription opioid use on antihyperglycemic medication adherence and the subsequent risk of developing diabetes related hospitalizations associated with non-adherence to antihyperglycemic medication, when both drugs are prescribed concomitantly.

1.3 Statement of Problem

Adherence to antihyperglycemic medication is a major factor in achieving adequate glycemic control. Chronic pain is a highly prevalent condition, as almost half of adults in the US with T2DM report acute and chronic pain (Francisco, 2012). Prescription opioids are the most prescribed class of medication for pain management with the number of prescriptions prescribed increased from 76 million in 1991 to 207 million in 2013 (Volkow & McLellan, 2016). Long-term use of prescription opioid is questionable as it can lead to adverse outcomes including ADRB patterns. Due to potential ADRBs, patients prescribed antihyperglycemics and prescription opioids concomitantly may be at risk for decreased adherence regarding their antihyperglycemic medication as these patients may become more focused on their prescription opioids rather than

other aspects of their treatment (Substance Abuse and Mental Health Services Administration, 2012). Non-adherence of antihyperglycemic medications can lead to increased T2DM related complications and subsequent hospitalizations.

1.4 Significance of Objectives

Prescription opioids are a highly prescribed class of medication, which when administered over long durations can lead to negative effects (e.g., addiction, non-medical use). Prescription opioids are often prescribed concomitantly with antihyperglycemic medication among patients with T2DM. Due to known associated negative effects of prescription opioids, it is imperative to study the impact of long term opioid use of antihyperglycemic medication when prescribed concomitantly. Therefore, the primary aim of this study was to examine if there is any effect of long-term opioid use on antihyperglycemic medication adherence when the two medication classes are prescribed concomitantly among patients with T2DM. Additionally, this study also examined whether the duration of opioid use and antihyperglycemic adherence has any potential impact on subsequent diabetes related hospitalizations.

CHAPTER TWO: LITERATURE REVIEW

2.1 Diabetes Mellitus

Diabetes Mellitus (DM) is a metabolic disorder which is characterized by the presence of hyperglycemia, which is a condition in which excessive amount of glucose circulates in the blood plasma (Reaven, 1988). DM is attributed to defective insulin secretion in the body, defective insulin action or a combination of both (American Diabetes Association, 2009). Unmanaged chronic hyperglycemia, among patients with DM can lead to micro vascular and macro vascular complications affecting different parts of the human body including eyes, kidneys and nerves (Guariguata et al., 2014).

DM is the most common metabolic disorders in the world and its prevalence has been increasing over the last two decades (Olokoba et al., 2012). Urbanization and its associated consequences are one of the prime reasons that has led to the increasing prevalence of DM. DM is the seventh leading cause of death in the US (Centers for Disease Control Prevention, 2011). According to the Centers for Disease Control and Prevention (CDC) estimates from the year 2014, found that 29.1 million Americans were diagnosed with diabetes, which accounted for approximately 9.3% of the US population (American Diabetes Association, 2012). According to 2012 estimates, 1.4 million Americans are newly diagnosed with diabetes each year (American Diabetes Association, 2012). Incidence rates of DM are highest among non-Hispanic blacks and Hispanic adults (Centers for Disease Control and Prevention, 2014).

2.2 Types of Diabetes Mellitus

In the 1979, an international workgroup sponsored by the National Diabetes Data Group of the National Institutes of Health (NIH) developed the classification of DM based on the

recommendations of various diabetes organizations (American Diabetes Association, 1979). According to the American Diabetes Association guidelines of 2010, diabetes has been classified as detailed below (American Diabetes Association, 1979).

Type 1 Diabetes Mellitus

Type 1 DM (T1DM) is also reffered to as insulin dependent DM. T1DM accounts for only 5–10% of those diagnosed with DM. It is more prevalent among children and young adults (American Diabetes Association, 1979). The etiology is associated with an autoimmune condition in the body. This autoimmune condition affects the ability of the pancreas to produce insulin naturally. Insulin is a hormone in the body that regulates the usage and storage of glucose and fat. A lack of insulin can lead to glucose build up in the blood, which would have otherwise been converted to energy and thus used by cells.

Type 2 Diabetes Mellitus

Type 2 DM (T2DM) accounts for 90–95% of those diagnosed with DM. It is also known as adult-onset or noninsulin-dependent diabetes. The etiology is based on a combination of factors including resistance to insulin in the body, scarce insulin production by the pancreatic beta cells, and excessive glucagon secretion. As a result of inadequate insulin, the body is less able to absorb glucose from the blood. Patients with T2DM often do not require additional insulin throughout their lifetime (American Diabetes Association, 1979).

2.3 Economic and Humanistic Impact of T2DM

T2DM has a significant impact on the US healthcare system. In 2012, the total cost associated with T2DM was $245 billion, of which $176 billion was attributed to direct medical

costs and $69 billion was attributed to indirect medical costs (American Diabetes Association, 2015). In 2012, there was a 41% increase in the direct medical costs of diabetes management from the year 2007, which was $174 billion (American Diabetes Association, 2013). Most of the increased costs associated with T2DM was seen among inpatient related care (43% of the total medical cost), prescriptions for managing T2DM related comorbidities (18%), antihyperglycemic prescription medications (12%), physician office visits (9%), and nursing facility stays (8%) (American Diabetes Association, 2015).

Medical expenditures among diabetics are 2.3 times higher compared to patients without diabetes (American Diabetes Association, 2013). Among the indirect expenditures, absenteeism, reduced productivity, disease related disability, and loss of productivity due to morbidity associated with T2DM were the major factors contributing to indirect treatment costs (American Diabetes Association, 2013).

Quality of life is an important parameter that evaluates the health status of a patient (Smith, Avis, & Assmann, 1999). The quality of life of a patient is measured by assessing physical and social functioning, and the perceived physical and mental well-being of a patient (Sischo & Broder, 2011). Patients with diabetes often feel challenged by their condition which can affect their day to day activity (Joslin Diabetes Center, 2014). A study was conducted by Wexler et al. that estimated the impact of medical comorbidities, depression, and treatment intensity on quality of life among patients with T2DM using the Health Utilities Index-III instrument. The study found that based on the scale, median health utility score among patients with T2DM was 0.70 (0 = death to 1.0 = perfect health). The study concluded that patients with T2DM have a substantially decreased quality of life in association with their symptomatic complications (Wexler et al., 2006). Another study by Paschalides et al. examined health-related quality of life in patients with T2DM and found

that patients with the T2DM had lower scores for quality of life and it had a significant impact on their activities of daily living (Paschalides et al., 2004).

2.4 Antihyperglycemic Medication Adherence

The American Diabetes Association (ADA) recommends glycosylated hemoglobin (A1C) <7% for management of T2DM (Nathan et al., 2009). It recommends the use of antihyperglycemic medications along with lifestyle modifications to achieve adequate glycemic control. Antihyperglycemic medications are agents that are used to lower blood glucose levels. The ADA and the American Association of Clinical Endocrinologists (AACE) recommended the use different antihyperglycemic agents used for management of T2DM Table 2.1 (Tsang, 2012). Approved medications for T2DM are available in oral and non-oral dosage forms. Medication prescribed for T2DM are given as monotherapy and in combination with other antihyperglycemic and non-antihyperglycemic agents for management of T2DM.

Table 2.1 Pharmacological agents used for the treatment of Type 2 Diabetes Mellitus

Drug Class	**Medications**	**Dosage Form**
Insulins	Insulin glargine	Injectable
Biguanides	Metformin	Oral
Sulfonylureas	Glipizide	Oral
Glinides	Nateglinide	Oral
Thiazolidinediones	Pioglitazone	Oral
Incretin mimetics	Exenatide	Injectable
Amylinomimetics	Pramlintide	Injectable
Alphaglycosidase inhibitors	Miglitol	Oral
DPP-4 inhibitors	Sitagliptin	Oral
SGLT2 Inhibitors	Dapagliflozin	Oral

Maintaining adherence to oral antihyperglycemic medications has been one of the primary strategies to achieving long-term glycemic control (Lau DT & DP, 2004). Non-adherent diabetic patients have higher glycosylated hemoglobin, higher levels of systolic and diastolic blood pressure, as well as higher levels of low-density lipoprotein cholesterol levels (Zhu et al., 2010). Among patients with T2DM, non-adherence to antihyperglycemic medications can lead to cardiovascular disorders such as coronary artery disease, congestive heart failure, diabetic coma, cardiac arrhythmia, thrombotic and embolic cerebrovascular disorders, ischemic heart disease, cardiac arrest, and peripheral vascular disease (Cziraky et al., 2015). The literature on T2DM has reported that factors such as prescription opioid abuse and overuse, economic factors, dosage complexity and external factors (e.g., relationship with a physician, living situation and family support) are responsible for non-adherence to antihyperglycemic medication among patients with T2DM (Martin, Williams, Haskard, & DiMatteo, 2005; World Health Organization, 2003).

The majority of adults diagnosed with T2DM use oral antihyperglycemic medications, along with lifestyle modification techniques such as a proper diet and exercise, to achieve adequate glycemic control (George & Copeland, 2013). Adherence rates for patients with T2DM have ranged from 65% to 85% for oral agents (Rubin, 2005). A recent meta-analysis examined overall rates of adherence for patients with T2DM who were prescribed oral antihyperglycemic agents and found that the pooled medication possesion ratio (MPR) was 75.3%, and the proportion of adherent patients was 67.9% (Iglay et al., 2015). Findings from the study suggested that adherence rates are suboptimal in patients with T2DM, who were prescribed oral antihyperglycemic medications.

2.5 Prescription Opioids

Opioids are chemical compounds that bind to opiate receptors (Rosenblum , Marsch, Joseph, & Portenoy, 2008). Opioids are alkaloid derivatives of opium poppy. Prescription opioids also include semi-synthetic opiates that are synthesized from naturally occurring opioids (e.g., heroin from morphine) (Cambridge Health Alliance, 2015; Filizola & Devi, 2012). Prescription opioids are also synthesized from synthetic opioids (e.g., methadone) (Rosenblum, Marsch, Joseph, & Portenoy, 2008).

Prescription opioids are typically used for pain management, cough and diarrhea (Centers for Disease Control and Prevention, 2016). Also, prescription opioids are frequently used in the management of acute to severe pain following surgery or other traumatic episodes. Moreover, prescription opioids are widely used in the treatment of pain related to cancer (Rosenblum et al., 2008).

In the US, numerous prescription opioids are approved for various therapeutic conditions. These include combination products, or single entity opioid medications as listed in Table 2.2 (Rosenblum et al., 2008). Promethazine/codeine is a combination antihistamine and opioid which is used for treating cough and other upper respiratory symptoms (Drugs.com, 2013).

Table 2.2 Opioid based single-entity and combination drugs

Opioid Based Drugs	
Drug Name	**Brand Name**
Single-entity opioid medication	
Morphine	Avinza®, Kadian®, MS Contin[a]®, MSIR®
Oxycodone	OxyContin®
Fentanyl	Duragesic®, Actiq®, Fentora®
Hydromorphone	Dilaudid®
Oxymorphone	Opana®
Combination based opioid medication	
Hydrocodone and Acetaminophen	Vicodin®, Lorcet®
Hydrocodone and Ibuprofen	Vicoprofen®
Tramadol and Acetaminophen	Ultracet®
Oxycodone and Acetaminophen	Percocet® or Percodan®

[a]MS - Morphine sulfate

2.6 Pain

Pain is an uncomfortable sensation in body that suggests that something is not functioning properly (Woolf, 1989). Pain can be described in many ways based on its type (Closs & Briggs, 2002). Receptor nerve cells that are in and beneath the skin can sense heat, cold, light, touch, pressure, and pain. The human body has thousands of receptor cells that can sense pain. When the body undergoes injury, these cells send messages along nerves into the spinal cord and then up to the brain. Prescription opioids are analgesics that act by blocking these messages or reduce their effect in the central nervous system (US Department of Health & Human Services, 2007). Pain is often associated with other symptoms, like nausea, dizziness, or weakness. Unmanaged pain can also lead to anger, depression, mood swings or irritability among some patients. Additionally, pain can also have a negative impact on a person's job performance, relationships and independence (Institute of Medicine, 2011).

Pain can be classified as either acute or chronic. Acute pain is often short-lived, and is a signal that the body has been injured. Chronic pain is present for long periods of time. Chronic

pain is often a result of a disease or a trauma from a past event (e.g., car accident) (Institute of Medicine, 2011). Chronic pain can be characterized as pain sensations in the human body over a prolonged duration and is defined by the International Association for the Study of Pain as ‘‘pain that persists beyond normal tissue healing time, which is assumed to be three months’’ (Roger Chou et al., 2009; Elliott, Smith, Penny, Smith, & Chambers, 1999). Chronic pain can be defined in various ways, therefore, there is no clear estimate of chronic pain prevalence in the US. A study by Clark et al. defined chronic pain as pain being present six months or more in the past year or as lasting at least three months (Clark, 2002). Some chronic pain definitions are based on the severity of pain (Gureje, Von Korff, Simon, & Gater, 1998). Another study by Elliot et al. has defined chronic pain as a painful sensation that acts as a deterrent to regular activities of daily living (Elliott et al., 1999). Based on the different definitions, current estimates of chronic pain have ranged from 12% to 25% (Gaskin & Richard, 2012; Goldberg & McGee, 2011). According to the Institute of Medicine, there are more than an estimated 100 million Americans that are suffering from chronic pain (Simon, 2012). Furthermore, according to a data from 2010, chronic pain cost the US $635 billion each year in medical treatment and lost productivity (Simon, 2012).

The global population is ageing rapidly and the number of elderly people (people over 65 years of age) will soon exceed that of children under the age of five (World Health Organization, 2012). Older people often live with conditions like arthritis, osteoporosis, back and/or cancer pain. Chronic pain contributes to disability, decreased mobility, depression, and impaired quality of life (Wright M, 2016). Chronic pain can be attributed to multiple factors. It can be caused by an injury, such as a back sprain or knee sprain, or it can be due to an illness affecting a patient. Studies have shown that pain is a common morbidity among patients who suffer from conditions like fatigue

and sleep disturbance (Matthews, 2011). Chronic pain impacts a patient's limb movements, and it leads to reduced flexibility, and decreased strength and stamina (H. y. Cho, Kim, & Kim, 2014).

2.7 Chronic Opioid Use

Prescription opioids are widely accepted for the treatment of moderate to severe acute pain and chronic pain related to active cancer (Rosenblum et al., 2008). Chronic pain can occur in the context of various diseases. All chronic pain disorders outside of cancer pain or pain at the end of life are known as chronic noncancer pain (CNCP). Prevalent CNCP conditions include back pain, osteoarthritis, fibromyalgia, and headache (Roger Chou et al., 2009; van Laar et al., 2012). Patients prescribed opioids continue to take prescriptions opioids until they achieve adequate therapeutic relief (Wachholtz, Foster, & Cheatle, 2015). In certain scenarios, patients continue to take prescription opioids over months for pain management. According to trends and risks of opioid use for pain (TROUP) study, chronic or long-term opioid use is defined as receiving opioid therapy for greater than 90 days during a calendar year without discontinuation (Sullivan et al., 2008).

Currently, chronic opioid therapy is recommended in the treatment of pain related to different conditions. These conditions include back pain, neuropathic pain, arthritis, depression and cough (Kreek, 1988). Opioid prescribing for CNCP has increased in recent years, despite limited evidence suppoting long-term effectiveness of prescription opioids over longer durations (Berland & Rodgers, 2012; Chou, Turner, Devine, & et al., 2015). One-third of adult Americans suffer from chronic pain, and 5% receive opioid treatment; moreover, strong opioids are prescribed in up to 9% of all office visits (Berland & Rodgers, 2012). Until the 1990s, physicians prescribed opioid treatment to patients following surgery or for cancer-related pain. However, studies during

the early 1990's showed that pain management was inadequate and as a result it led to an increase in opioid prescribing for patients with CNCP (Franklin, 2014).

A review of the literature on prescription opioids suggests that there has been an excessive increase in opioid utilization for CNCP. Although some patients benefited from increased prescription opioid use for CNCP, there are significant negative effects associated with long-term use. The literature on opioid use also suggests that drug tolerance has been seen among patients in as little as two weeks of continuous opioid use (Berland & Rodgers, 2012).

Prescription opioids are also used as antitussive agents. Dextromethorphan is a synthetic opioid, which is used as an over-the-counter cough suppressant. Codeine preparations have been extensively used for cough management but their clinical efficacy is less certain when prescribed over longer durations. For chronic cough management, codeine and hydrocodone preparations over a long duration are recommended for cough suppression, though long-term use of prescription opioids is associated with major concerns (Dickinson, Morjaria, Wright, & Morice, 2014; Stolz et al., 2004).

2.8 Problems Associated with Chronic Opioid Use

Prescription opioids are the most prescribed medication class for management of chronic pain (Rosenblum et al., 2008). Over the past two decades, there has been a tremendous increase in the utilization of prescription of opioid medications for chronic pain, despite limited evidence showing long-term beneficial effects (Noble et al., 2010; M. D. Sullivan et al., 2008). Some of the major issues associated with chronic prescription opioid use are detailed in the following text (Clark M, 2012).

Accidental Overdose and Death

Prescription medications are only safe if taken as directed. An overdose of prescription opioid medication can result in death due to opioid overdose (Rosenblum et al., 2008). Combining opioids with alcohol, sleep aids or muscle relaxers increases the risk of overdose and death.

Physical Dependence

Chronic use of prescription opioids for pain management leads to addiction or dependence. Physical dependence leads to drug withdrawal symptoms when a patient stops taking the drug. With psychological dependence a patient feels a strong craving for the drug. Alcohol use with prescription opioids can also lead to physical dependence.

Tolerance

Over time, patients increase their dose of prescription opioid pain medicine to get the same amount of relief. This effect of decreased relief over long-term use of prescription opioids is refered as tolerance. Tolerance is common with the long-term use of prescription opioid as pain receptors become less sensitive to opioids over time (Rosenblum et al., 2008). At some point, increasing the dose of medication will not provide adequate pain relief due to the ceiling effects of the medication (Rosenblum et al., 2008). Due to the ceiling effect, patients often require higher doses of prescription opioids to receive the adequate relief from pain. Increased doses lead to increased risk of side effects and complications.

Breathing and Heart Problems

Slower breathing rate is observed among patients with chronic opioid use. It can also stop breathing altogether which can lead to death (Walker et al., 2007). Chronic prescription opioid use

can cause irregular heart rhythms which can be life threatening at times (Macey, Weimer, Grimaldi, Dobscha, & Morasco, 2013).

Sleep Disorders

Sleep apnea is a condition identified by long breathing gaps while a patient is sleeping (Walker et al., 2007). This leads to low levels of oxygen in the body which can in turn damage heart and lungs (Khoo, Kronauer, Strohl, & Slutsky, 1982). Chronic prescription opioid use can increase the risk of sleep apnea (Walker et al., 2007).

Opioid-induced Hyperalgesia

Chronic prescription opioid-induced hyperalgesia is a condition where opioid medications create more pain rather than pain relief (Hay et al., 2009).

Increase Risk of Fracture

Prescription opioid use can also affect bone health. Prescription opioids use over a long duration can develop osteoporosis. Osteoporosis leads to an increased risk of bone fractures among long-term prescription opioid users (Daniell, 2004).

2.9 Chronic Pain and T2DM

The elderly population often suffers from conditions like arthritis which causes pain to different parts of the body. Primarily chronic pain is mainly due to lower back pain and osteoarthritis pain (Johannes, Le, Zhou, Johnston, & Dworkin, 2010). Chronic pain is a problematic comorbid condition often seen among patients with T2DM. The prevalence of chronic pain among those with T2DM ranges from 10% to 42%, and it causes a significant amount of disability (Tunks, Crook, & Weir, 2008).

2.10 Pharmacologic Management of Chronic Pain

Chronic pain is characterized by symptoms such as limited mobility, low physical functional status, and disturbed sleep patterms. Furthermore, chronic pain can also cause depression and anxiety. The management of chronic pain can be addressed by a combination of pharmacological agents and also non-pharmacological methods (Ambrose & Golightly, 2015).

Pharmacological drug classes used to treat chronic pain include NSAIDs, acetaminophen, corticosteroids, prescription opioids, antidepressants, and anticonvulsants (American Chronic Pain Association, 2015). NSAIDs (e.g., aspirin, ibuprofen) work body by reducing the production of prostaglandins (pro-inflammatory chemicals). Prostaglandins are pro-inflammatory chemical compounds which are produced when a patient is in the processes of inflammation, pain, and/or fever (Pain Community Center, 2015). Tricyclic anti-depressants and serotonin–norepinephrine reuptake inhibitors (SNRIs) work by blocking pain messages conducted to the brain, and are also believed to stimulate the release of endorphins, which are the body's natural painkillers (Toft DJ, 2014). Anticonvulsants help in pain management of chronic pain by slowing down nerve signals so that the pain-related nerve signal is not transmitted as efficiently (Toft DJ, 2014). Actions of prescription opioids are mainly inhibitory in nature. The presynaptic action of opioids to inhibit neurotransmitter release is considered to be their primary mechanism of action. This inhibition of neurotransmission results in hyper polarization and a reduction in neuronal excitability, thus resulting in decrease of pain (McDonald & Lambert, 2014).

2.11 Barriers to Antihyperglycemic Medication Adherence

Poor antihyperglycemic medication adherence contributes to suboptimal glycemic control, which acts as a major barrier to effective diabetes management (Wroth & Pathman, 2006). Low adherence to prescribed antihyperglycemic medications accounts for 30% to 50% of treatment failures, leading to adverse treatment outcomes which can cause damage to vital organs (Abebe, Berhane, & Worku, 2014). Treatment failure is in turn associated with reduced treatment benefits and can have a negative financial burden on both patient and society as a whole. Many factors affect antihyperglycemic medication adherence among patients who are prescribed prescription opioids and antihyperglycemic medications concomitantly.

Polypharmacy

Studies have found that patients who are on multiple drugs often have difficulty managing their medications, which can lead to adverse drug events (ADEs) and nonadherence to medications. A recent report by the Medicare payment advisory commission (MedPAC) suggested that ADEs are often associated with opioid use, mainly due to patients taking multiple drugs (polypharmacy) and because prescription opioid use itself can lead to many ADEs, including unintentional overdoses (The Medicare Payment Advisory Commission, 2015). Therapeutic competition occurs when treatment for one medical condition adversely affects another condition. Opioid-related therapeutic competition is a side effect of polypharmacy (The Medicare Payment Advisory Commission, 2015). One of the most common side effects of prescription opioid is constipation. Studies have shown that about 40 percent of patients prescribed prescription opioids as an analgesic have experienced constipation and other gastrointestinal effects (Panchal, Müller-Schwefe, & Wurzelmann, 2007).

Prescription Opioid-related Aberrant Drug Behavior

Use of prescription opioids for CNCP remains controversial (Cowan, Wilson-Barnett, Griffiths, & Allan, 2003). There is a dearth of literature on the long-term effectiveness of prescription opioids for CNCP. Most of the literature is inconclusive about the long-term efficacy of prescription opioids (R. Chou, G. J. Fanciullo, P. G. Fine, J. A. Adler, et al., 2009). Although extensive clinical experience suggests that prescription opioids can improve pain and function in some patients, a significant proportion of patients experiences no improvement in functionality. Also, opioid use is associated with a variety of potentially serious adverse outcomes which includes harms related to drug abuse and diversion (R. Chou, G. J. Fanciullo, P. G. Fine, C. Miaskowski, et al., 2009).

Aberrant drug-related behaviors (ADRBs) refers to drug taking behavior outside clinical expectations that may indicate substance misuse, abuse, or addiction. ADRBs can be due to factors like undertreated pain or a patient's misunderstanding of the dosage regimen. According to a recent article by the Substance Abuse and Mental Health Services Administration (SAMHSA) on chronic opioid use, it stated that at some point in the treatment of chronic pain, patients on prescription opioids are likely to fail to adhere to their treatment agreement. Failing to adhere to the regimen prescribed due to prescription opioid is indicative of ADRBs among those using prescription opioids. Patients with ADRBs often become more interested in their prescription opioid medication than in other medications (e.g., antihypertensive) or in any other aspect of treatment (e.g., exercise) (Substance Abuse and Mental Health Services Administration, 2012).

Patients with ADRBs often demonstrate behavior whereby patients take larger doses of prescription opioids than what their prescribed intended. Patients exhibiting ADRBs may also

insist on being prescribed higher doses of prescription opioids. These patients typically resist drug screening tests that detect for higher than normal prescription opioid concentration in the body. Patients with ADRBs repeatedly lose their opioid medications and seek early refills for prescription opioids. Patients with ADBRs are also involved in obtaining opioid medications illegally (e.g., from multiple clinicians, street dealers, family members, the Internet, forged prescriptions) (Substance Abuse and Mental Health Services Administration, 2012).

Impulsivity and Prescription Opioid Use

Impulsivity is defined as choosing a smaller reward that may be obtained immediately over a larger reward that may not be obtained immediately (Białaszek, Gaik, McGoun, & Zielonka, 2015). Logue et al. extended impulsivity theory by including all choices that result in small immediate rewards but delayed unpleasant consequences (Logue, 1995). Looking at opioid abuse through the lens of impulsivity, it reflects that substance abuse can be best described as a series of impulsive choices (Madden, Petry, Badger, & Bickel, 1997). Impulsive choices may predominate in prescription opioid users who forego a variety of tangible and social rewards for relatively brief but immediately available bouts of drug intoxication or avoidance of transient withdrawal symptoms (Madden et al., 1997).

Use of prescription opioids is associated with increased impulsivity, risky decision making, and impaired behavioral control (Madden et al., 1997). This behavior has been explained in the model of patient behavior (Madden et al., 1997; Myerson & Green, 1995). It postulates that this decrease in value as a function of delay is termed temporal discounting. Temporal discounting states that a smaller, more immediate reward may be chosen because the current worth of the larger, more delayed reward is discounted; hence, the delayed reward's current value may be lower than that of the more immediate reward (Myerson & Green, 1995).

Like other substance abusers, prescription opioid abusers are also impulsive regarding their decision making and hence prefer short-term immediate rewards in the form of intoxication and forego long-term health rewards otherwise associated with the drug (Madden et al., 1997).

Socioeconomic Factors and Prescription Opioid Use

Prescription drug spending in 2007 was greater than $750 per capita in the U.S., of which patients must pay a growing percentage of prescription drug share through medication copayments (Kurlander, Kerr, Krein, Heisler, & Piette, 2009). In 2007-2008, nine out of ten older adults used prescription medications once a month (Qiuping Gu, 2010). Low-income patients take their medications despite paying for copayments; however, one-fifth of those patients do not take medications because of cost. Thus, cost-related nonadherence to medications has been associated with increased rates of serious adverse events, emergency department visits, hospitalizations, and poorer health (Kurlander et al., 2009).

Kurlander et al. found that of patients who were prescribed prescription opioids and antihyperglycemic medications, 9% cut back on medications for both conditions, 13% cut back on antihyperglycemic medications alone, and 9% cut back on opioids alone (Kurlander et al., 2009). The study found that lower income and higher out-of-pocket medication costs significantly increased the odds that diabetic patients would report cost-related non-adherence (Piette, Heisler, & Wagner, 2004).

Need to Treat Symptomatic Conditions

Chronic pain is a comorbid condition that could be especially troublesome for patients with diabetes given its symptomatic manifestation and the accompanying psychological distress and physical disability. A study by Krien et al. found that among patients with T2DM and chronic pain,

it has been seen that chronic pain affects self-management of T2DM (S. L. Krein, M. Heisler, J. D. Piette, F. Makki, & E. A. Kerr, 2005). Patients with T2DM and chronic pain have symptomatic and asymptomatic symptoms due to their disorder. Symptomatic conditions include pain whereas asymptomatic symptoms include increased glucose level. Taking into account the previous factors that can cause non-adherence to antihyperglycemic medications along with a diabetic patients need to manage the symptomatic discomfort of pain first, patients may often prefer to take their prescription opioids as opposed to their antihyperglycemic medication (S. L. Krein et al., 2005).

This study was conducted using 2003-2004 MarketScan® Commercial Claims and Encounters Database (Commercial). Enrollees in this database were employees, and their dependents covered by the employer-based health insurance. Medical claims of patients were linked through a unique identifier obtained in the datasets.

2.12 Theory of Rational Addiction

Several economic and noneconomic approaches to understanding substance abuse disorders have focused on how delayed outcomes are discounted in value among patients who abuse substances. For example, to explain why an alcoholic chooses to drink over abstinence from alcohol, economic theory suggests that the rewards of sustained abstinence and the future costs of current drinking are discounted to a high degree. Therefore, subjective value of these costs and benefits are minimized relative to the value of the immediate rewards of drinking. The theory of rational addiction (Becker & Murphy, 1988), is based on exponential discounting of delayed consequences (Becker & Murphy, 1988). According to the theory of rational addiction, substance abusers make rational decisions to maximize utility and, in doing so, consider the full cost of using drugs when choosing between drug use and abstinence. The total cost of drug use includes a variety

of factors including the monetary cost of the drug and the delayed, probabilistic, harmful consequences of drug use. Rationally, the benefits of abstinence outweigh the costs associated and would seem to favor abstinence (Becker & Murphy, 1988).

According to the theory, patients using opioids are more impulsive in their decision-making. A study by Madden and colleagues explained the basis for decision making when patients are on opioids (Madden et al., 1997). Among patients on opioids, impulsivity leads to choices that result in small immediate rewards but it may have delayed unpleasant consequences. Similarly, among chronic opioid users, impulsive choices predominate and thus users forego delayed tangible and social rewards. The study found that opioid users had a higher discounting, which is due to impulsivity associated with opioid use. Therefore, according to the theory, a patient who wants to abuse seeks immediate reward (e.g., intoxication, euphoric experience) over delayed positive effects of the event. These findings in the contextof this study, suggest that patients, when prescribed antihyperglycemic medications and prescription opioids concomitantly might experience impulsivity due to long-term opioid use. This may negatively impact a patient's medication taking behavior.

2.13 Complications of Non-adherence to Antihyperglycemic Medication

Diabetes increases the risk for many serious health problems. Maintaining adherence to oral antihyperglycemic medications is essential in achieving long-term glycemic control among most patients with T2DM. Non-adherence to antihyperglycemic medications can lead to short-term, and long-term complications among patients with T2DM (EndocrineWeb, 2016). These complications develop over years and they are associated with how blood glucose levels can affect blood vessels. Elevated levels of blood glucose can damage the blood vessels, both small and large.

Long-term complications of T2DM related disorders include retinopathy, kidney disease (nephropathy), diabetic neuropathy, and macro vascular problems. Macro vascular complications among patients with T2DM can affect large blood vessels, causing plaque to build up over time and potentially leading to a heart attack, stroke or vessel blockage in the legs (EndocrineWeb, 2016).

The current literature on T2DM and hospitalization risk suggests that patients who do not adhere (i.e., take medication) to at least 80% of their oral antihyperglycemic medications across one year are at a higher risk of hospitalization in the following year (Blackburn et al., 2013). It also leads to increased healthcare resource utilization. Even with the presence of existing evidence regarding antihyperglycemic medications and subsequent hospitalization risk, there is a lack of literature to examining whether concomitant prescribing of prescription opioids and antihyperglycemic medications can negatively impact antihyperglycemic medication adherence and thus lead to subsequent diabetes related hospitalizations.

CHAPTER THREE: MANUSCRIPT 1

IMPACT OF LONG-TERM OPIOID MEDICATION USE ON ORAL ANTIHYPERGLYCEMIC MEDICATION ADHERENCE AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS

3.1 Abstract

Introduction: Adherence to antihyperglycemic medication is imperitive to accomplish adequate glycemic control among patients with T2DM. Chronic and neuropathic pain causes hindrance to achieving the glycemic goal among patients with T2DM. This analysis compares adherence to antihyperglycemic medications among patients with T2DM, who are concomitantly prescribed opioids.

Methods: This retrospective cohort study utilized the 2003-2004 US MarketScan® (Truven Health Analytics, Ann Arbor, MI, USA) Commercial health insurance claims data. Adults aged 18 years with T2DM who received prescription opioids were included. Adherence to antihyperglycemic medications was calculated among long-term (≥ 90 days) opioid users and short-term (< 90 days) opioid users who were prescription opioid naïve in the baseline period. Adherence was measured using the proportion of days covered (PDC), with PDC of ≥ 0.80 considered adherent. Multivariable logistic regression was used to predict antihyperglycemic medication adherence between the cohorts, while controlling for baseline differences.

Results: There were 22,212 patients with T2DM, of which 7,294 (32.8%) were long-term opioid users, and 14,918 (67.2%) were short-term opioid users. During the 6-month follow-up, long-term opioid users were 1.37 times more likely to be adherent to their antihyperglycemic medication therapy as compared to short-term opioid users (OR = 1.37, 95% CI = 1.28-1.47).

Conclusion: Adherence to antihyperglycemic medication increased after patients initiated prescription opioids. Patients with T2DM who were prescribed long-term prescription opioids as compared to short-term prescription opioids were more adherent to their antihyperglycemic medications.

3.2 Background

Opioid analgesics are widely accepted as one of the most effective medication class for the management of pain. Prescription opioids were initially prescribed for pain management among patient's post-surgery and among patients with cancer. Opioids are now considered one of the most potent and efficient drugs for the management of non-cancerous acute and chronic pain, treating both moderate to severe conditions (Savage, Kirsh, & Passik, 2008). The use of opioids for pain management has increased significantly in the US over the last two decades (Laxmaiah Manchikanti, 2012). The amount of prescription opioids prescribed for pain management has increased significantly in the past 20 years for chronic pain management despite limited evidence demonstrating the long-term beneficial effects (Volkow & McLellan, 2016). In the US, the number of prescriptions for opioids (e.g., hydrocodone) escalated from 76 million in 1991 to approximately 207 million in 2013 (National Institute of Drug Abuse, 2014). The US has become the biggest consumer globally of opioids based medications. Furthermore, the US accounts for almost 100 percent of hydrocodone and 81 percent for oxycodone prescribed globally in the year 2013 (National Institute of Drug Abuse, 2014).

Greater availability and increased prescribing of prescription opioids is associated with increases in abuse related to these medications. For example, the number of emergency department (ED) visits involving the non-medical use of opioid analgesics doubled from 144,600 in 2004 to

305,900 in 2008 (National Institute of Drug Abuse, 2014). Prescription opioid-related overdose deaths have more than tripled during the last 20 years (National Institute of Drug Abuse, 2014). In 2010, 16,651 people died because of prescription opioid-related overdose in the US (Behavioral Health Coordinating Committee - Prescription Drug Abuse Subcommittee, 2013). The mechanism of action of prescription opioids is similar to that of heroin, as they both impact the human brain by generating a surge of euphoria upon usage. The onset and intensity of euphoric experience varies by the route of administration and formulation. However, all prescription opioids when not taken as prescribed by patients can cause physical dependence, abuse, and addiction. (National Institute of Drug Abuse, 2014).

Opioids for Chronic Pain

Chronic pain affects approximately one-third (100 million) of US adults, and five percent of these patients suffering with chronic pain receive opioid treatment for pain management (National Institute of Drug Abuse, 2014). Use of prescription opioids has increased significantly, as one study suggests that the use of strong opioids (e.g, oxycodone) is seen in up to nine percent of all office visits (Berland & Rodgers, 2012). A significant number of patients with chronic pain are prescribed opioids over long durations. Currently, most literature does not support the use of long-term opioids for chronic pain management (Chou et al., 2015). Studies report that long-term opioid use is associated with diversion and deaths due to the non-medical use of prescription opioids (Compton, Jones, & Baldwin, 2016). Pain is a comorbid condition that affects 40% of patients with T2DM (Rebecca L. Sudore et al., 2012). For most of these people, the pain is chronic, defined as pain persisting for more than 90 days (Valkanoff, Kline-Simon, Sterling, Campbell, & Von Korff, 2012). Among diabetics, pain can be neuropathic pain from diabetic peripheral neuropathy or non-neuropathic pain which includes musculoskeletal conditions, such as

osteoarthritis, shoulder disorders, and lower back pain (Averyt, 2012). Regardless of the cause, previous literature suggests that chronic pain can affect diabetes self-management.

Non-medical Use of Prescription Opioids

The non-medical use of prescription opioids is a significant problem in the US. It is characterized by using opioid analgesics more than they were prescribed, or obtaining them without a prescription from sources other than pharmacies. Non-medical use of prescription opioids is typical when patients want to experience euphoric sensations (Compton et al., 2016). In 2014, non-medical use of prescription opioids was reported by 10.3 million patients (Compton et al., 2016). ED visits due to the non-medical use of prescription opioids increased 153% between 2004 and 2011. In the last decade, the rates of death due to non-medical use of opioids have rose from 1.5 to 5.9 per 100,000 people (Compton et al., 2016). According to a recent article by the Substance Abuse and Mental Health Services Administration (SAMHSA) on chronic opioid use, it stated that at some point in the treatment of chronic pain, patients are likely to fail to adhere to their treatment agreement. Patients using opioids over longer durations demonstrate aberrant drug-related behaviors (ADRBs). ADRBs refers to drug taking behaviors which demonstrate substance misuse, abuse, or addiction. Patients with ADRBs are often more interested in prescription opioids than in their other medication treatment(s) (Substance Abuse and Mental Health Services Administration, 2012).

Antihyperglycemic Medication Adherence and Barriers to Adherence

Adherence to antihyperglycemic medications is a primary factor required to achieve adequate glycemic control among patients with T2DM. Non-adherence to antihyperglycemic medication is attributed to 30% to 50% of the patients who don’t achieve adequate glycemic

control from their prescribed antihyperglycemic, which leads to poorer health outcomes (Abebe et al., 2014). Several factors that can affect adherence to oral antihyperglycemic medications have been identified in the literature. These factors include younger age, female gender, patients living in the Southern region of the US, polypharmacy, socioeconomics factors, and high cost-sharing is associated with lower adherence to oral antihyperglycemic medications. With ADRBs associated with long-term users of prescription opioids, it can potentially affect adherence to diabetic medication when taken concomitantly.

To our knowledge, no previous study has examined the impact of opioid use on antihyperglycemic medication adherence when prescribed concomitantly. Considering the ADRBs associated with long-term opioid use, it is imperative to study the effect of long-term prescription opioid use when prescribed concomitantly with antihyperglycemic medications. This study compared the adherence of oral antihyperglycemic medication among patients with T2DM who are prescribed long-term (≥90 days) and short-term (less than 90 days) of prescription opioids.

3.3 Methods

Data Source

Administrative claims data from the Truven Health MarketScan® (Truven Health Analytics, Ann Arbor, MI, USA) was used to address the objective of this study. MarketScan® data is collected from employers, health plans, and state Medicaid agencies. MarketScan® consists of three core claims databases, a hospital discharge database as well as several linked databases, data sets, and files that link claims data to other patient and employee data at the patient level.

This study was conducted using 2003-2004 MarketScan® Commercial Claims and Encounters Database (Commercial). Enrollees in this database were employees, and their

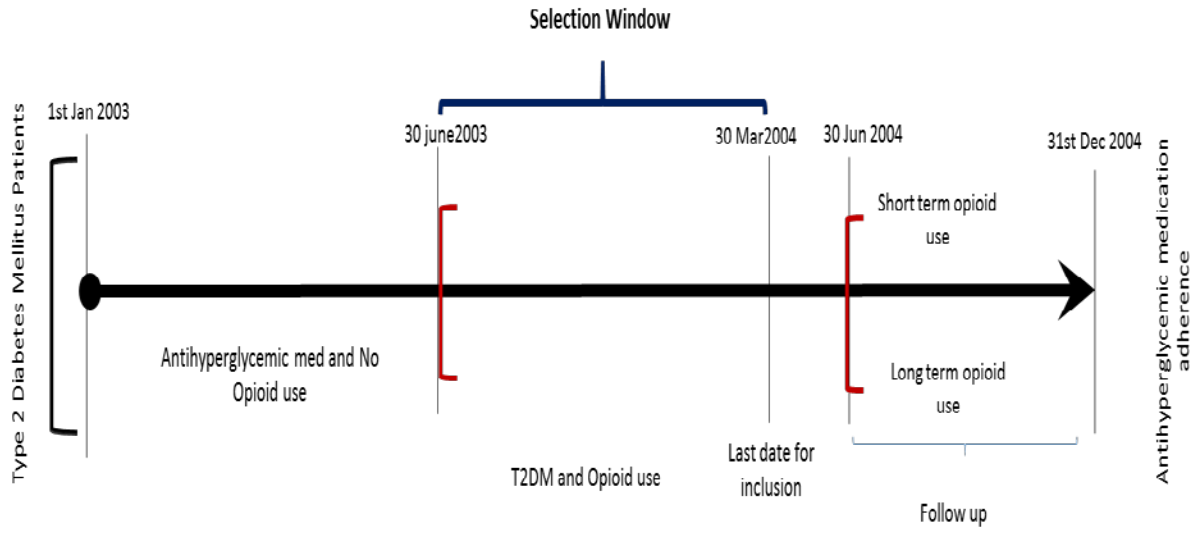
dependents covered by the employer-based health insurance. Medical claims of patients were linked through a unique identifier obtained in the datasets.

3.4 Sample and Study Design

Patients aged 18 years and older were included in this study. Patients were required to be continuously enrolled for the study duration and have at least one non-diagnostic medical claim with a T2DM diagnosis ([ICD-9-CM] 250.x0, 250.x2) in the baseline and follow-up period. Also, these patients were required to have at least one outpatient pharmacy claim with a National Drug Code (NDC) for an antihyperglycemic medication (e.g., sulfonylureas, biguanide). Patients with Type 1 diabetes mellitus, diabetes in pregnancy and disease conditions where opioids are prescribed for non-diabetes related pain management were also excluded (e.g., cancer, fibromyalgia, falls and fractures, surgeries).

According the to the study design in Figure 3.1, patients with T2DM and an antihyperglycemic medication claim and no prescription opioid claim were identified in the first six months of study. Of these, patients with an antihyperglycemic medication claim and prescription opioid claim were selected in the patient's accrual window. Prescription opioid persistence was measured over 90 days among patients from their first claim of prescription opioid, in order to classify them as long-term opioid users ($\geq$ 90 days) and short-term opioid users ($<$ 90 days). Subsequent adherence to antihyperglycemic medication was measured over six months from the day the patient was classified as long-term or short-term user of prescription opioids.

Figure 3.1 Study design



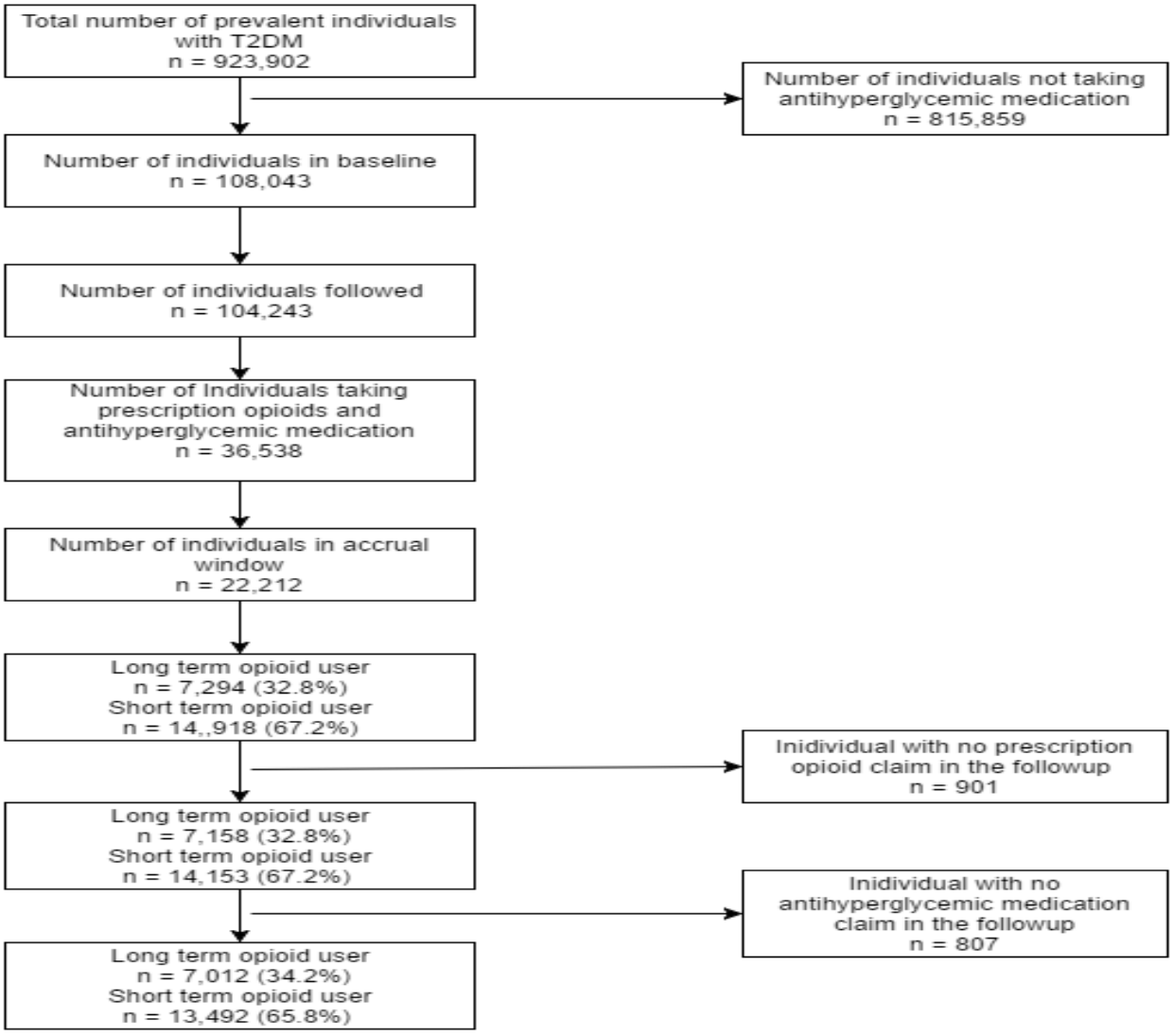
3.5 Statistical Analysis

For descriptive analyses, frequencies were measured for all study variables. A pairwise t-test was conducted to estimate the difference in antihyperglycemic medication adherence before and after opioid use for the same inidividual. A multivariable logistic regression model was used to compare the odds of being adherent to antihyperglycemic medication. Logistic models controlled for age, gender, region, plan type, capitated payment, baseline diabetes adherence, elixhauser comorbidity score for non-diabetes related severity and adapted diabetes complications severity index (aDCSI) score for diabetes-related severity. A sensitivity analysis was conducted by defining the long-term opioid use as greater than 60 days, with a maximum discontinuation of 5 days. A second sensitivity analysis was conducted among patients who were adherent to antihyperglycemic medication in the baseline period (PDC $\geq$ 0.80). An a priori alpha level of 0.05 was used to determine statistical significance. Analyses were conducted with SAS version 9.3 (SAS Institute Inc. Cary, NC, USA).

3.6 Patient Selection

As seen in Figure 3.3, for the analysis, 923,902 patients were identified with T2DM. After meeting all tcriteria, there were 22,212 patients in the selection window; 7,294 (32.8%) were long-term opioid users, and 14,918 (67.2%) were short-term opioid users.

Figure 3.2 Patient attrition flow chart



3.7 Results

Descriptive Statistics

According to Table 3.1, mean age for patients with long-term opioid use was 55.82±6.52, years and mean age for patients with short-term opioid usage was 53.13±7.87. The majority of long-term opioid users were male (53.51%) whereas most of the patients using short-term opioids were female (52.13%). Mean non-diabetes severity reported through the elixhauser index was 0.12±1.10 for long-term opioid users, and was 0.13±1.06 for short-term opioid users. Mean diabetes severity was 0.80±0.32 for long-term opioid users and 0.78±0.37 for short-term opioid users.

Table 3.1 Frequency and distribution of patient demographic charecteritics

	Long-term opioid users		Short-term opioid users		P-Value
	n = 7,012		n = 13,492		
	Mean	SD	Mean	SD	
Age, years	55.82	6.52	53.13	7.87	0.001
Clinical characteristics					
aElixhauser Index[a]	0.12	1.10	0.13	1.06	0.85
aDCSI[b]	0.80	0.32	0.78	0.37	0.56
	N	%	N	%	
Gender					
Male	3,752	53.51	6,459	47.87	<0.001
Female	3,260	46.49	7,033	52.13	<0.001
Region					
Northeast	550	7.84	599	4.44	<0.001
North Central	2,501	35.67	4,018	29.78	<0.001
South	2,394	34.14	6,488	48.09	<0.001
West	1,567	21.62	2,387	17.10	<0.001
Insurance plan type					
Basic and comprehensive plans	1,801	25.68	2,347	17.40	<0.001
CDHP and HDHP[c]	2,464	35.14	4,481	33.21	<0.001
Capitated plan	2,724	38.85	6,627	49.12	<0.001
Non-capitated plan	23	0.33	37	0.27	<0.001
Presence of Capitated payment					
Capitated	1,112	15.86	1,373	10.18	<0.001
Non-capitated	5,899	84.14	12,108	89.82	<0.001

[a] Adapted Elixhauser Index

[b] Adapted diabetes severity comorbidity index

[c] Consumer-directed health plan/high-deductible health plan

Opioid Persistence

Patients were defined as a long-term or short-term users of prescription opioids based on their persistence to opioid medications. As seen in Table 3.2, 32.38% of opioid users in the cohort were long-term users and 67.16% were short-term users.

Table 3.2 Opioid persistence for patients in the follow-up period

Numbers of patients (Total = 22,212)	
Duration	N (%)
Long-term opioid use (≥90 days)	7,294 (32.84)
Short-term opioid use (< 90 day)	14,918 (67.16)

Adherence to Antihyperglycemic Medication

Mean adherence for patients in the baseline period (n= 108,043) was 0.68±0.25. As seen in Table 3.3, of these patients who had long-term opioid use (n = 7,012) their baseline 6-month antihyperglycemic adherence was 0.76±0.22, and their 6-month antihyperglycemic adherence in the follow-up period was 0.84±0.20. For patients in the short-term opioid user group (n = 13,492), their baseline 6-month antihyperglycemic adherence was 0.67±0.25, and their 6-month antihyperglycemic adherence in the follow-up period was 0.76±0.24.

Table 3.3 Antihyperglycemic adherence in the baseline and follow-up period

Opioid therapy duration	Baseline Duration PDC[a]	Follow-up Duration PDC
Long-term opioid use	0.76±0.22	0.84±0.20
Short-term opioid use	0.67±0.25	0.76±0.24

[a]PDC – Proportion of days covered

Pairwise t-test results (Table 3.4) shows the difference in the adherence scores for patients in the baseline and follow-up. Findings demostrated that there was a significant difference between baseline and follow-up adherence scores.

Table 3.4 Pairwise t-test to compare antihyperglycemic medication adherence at baseline and follow-up

Opioid therapy duration	Total number of patients	DF	t-statistic	P-Value
Long-term opioid users (≥ 90)	7,012	7,011	-23.52	<0.0001
Short-term opioid users (< 90)	13,492	13,491	-37.56	<0.0001

Multivariable Logistic Regression Analysis

Table 3.5 presents adherence results among users who were concomitantly prescribed long-term or short-term prescription opioid therapy. In the adjusted logistic regression model, patients who were long-term opioid users were more adherent to their antihyperglycemic medication than short-term opioid users. During the 6-month follow-up, long-term opioid users (OR =1.37, 95% CI = 1.28-1.47) were 1.37 times more adherent to their antihyperglycemic medication therapy as compared to short-term opioid users. Females (OR = 0.89, 95% CI = 0.84-0.95) were less adherent to antihyperglycemic medication adherence as compared to males. Patients in the age group of 31 to 45 years (OR = 1.52, 95% CI = 1.11-2.10), 46-60 years (OR = 2.59, 95% CI = 1.90-3.54), and patients above 60 years (OR = 3.23, 95% CI = 2.36-4.34) were more adherent to antihyperglycemic medications as compared to patients in the age group of 18 to 30 years.

Table 3.5 Multivariable logistic regression to estimate predictors of antihyperglycemic medication adherence

Parameter	Odds Ratio	95% Wald's Confidence Limits		P Value
Opioid Use (Ref = Short-term opioid use)				
Long-term opioid use	1.37	1.28	1.47	<.01
Gender (Ref = Male)				
Female	0.89	0.84	0.95	0.02
Region (Ref = Northeast)				
North central	1.15	0.99	1.32	0.06
South	0.98	0.85	1.12	0.75
West	0.90	0.76	1.07	0.23
Age Category (Ref = 18 – 30 years)				
31- 45 years	1.52	1.11	2.10	0.01
46 - 60 years	2.59	1.90	3.54	<.01
Greater than 60 years	3.23	2.36	4.34	<.01
Health Plan Type (Ref = Basic and comprehensive plans)				
Non capitated plan	0.81	0.74	0.90	<.01
Capitated plans	0.88	0.80	0.96	0.01
CDHP and HDHP[a]	0.87	0.50	1.50	0.61
Capitated Service (Ref = No)				
Yes	1.23	1.05	1.43	0.01
Non-diabetes Severity index				
aElixhauser index[b]	0.97	0.95	1.00	0.05
Diabetes Severity Index				
aDCSI[c]	0.94	0.86	1.02	0.15
Baseline Antihyperglycemic Adherence				
Baseline antihyperglycemic adherence	15.08	13.26	17.16	<.01

[a] Consumer-Driven Health Plan/High Deductible Health plan
[b] Adapted Elixhauser Index
[c] Adapted diabetes severity comorbidity index

3.8 Discussion

Use of long-term opioids has been under scrutiny because of limited evidence demonstrating the effectiveness of opioids for chronic pain or other conditions. The results of this study suggest an increase in antihyperglycemic medication adherence among patients with T2DM in both short-term and long-term opioid use. The results were inconsistent with findings from the SAMHSA long-term opioid use guideline which suggests that concomitant use can affect the adherence to other medications.

The results from the multivariable analysis suggested that long-term users of prescription opioids were more adherent to their antihyperglycemic medication as compared to short-term opioid users. Although, the results were not consistent with SAMHSA opioid use guideline, the results were in accordance with the existing literature which suggests that long-term opioid users tend to better manage their pain, which in turn helps them manage their T2DM more effectively. In a study by Guerriero et al., patients with long-term opioid use managed their pain other conditions better than patients not receiving opioid therapy. Similar findings were reported by Krien et al., in that better management of chronic pain (i.e., taking pain medication) seemed to improve diabetes self-management. However, long-term use of prescription opioids is associated with serious health consequences and can lead to addiction, dependence or aberrant drug taking behaviors.

A few limitations related to this study should be discussed. Administrative claims data is primarily collected for billing and reimbursement purposes by health care plans and not necessarily for research. Data entry errors are common among these administrative databases. As this was a retrospective observational analysis, causal inferences should not be drawn. The calculation for adherence was based on days' supply and service dates, but this does not confirm whether the

patient ingested the medication. Also, with prescription opioids, there are many cash payments (i.e., non-insurance), which cannot be calculated using this database. Further, the years of available data was somewhat limiting. Therefore, examining medication adherence over a longer follow-up period was not possible. The database used for this study is not recent, thus limiting any medications approved at a later date. As this data is limited to individuals on commercial health plans, findings from the study may not be generalizable to the entire US population.

3.9 Conclusion

Patients using long-term opioid therapy were more adherent to their antihyperglycemic medication as compared to patients using short-term opioid therapy when prescribed concomitantly with antihyperglycemic medications. Sensitivity analyses also produced similar findings. Results from this study did not demonstrate any decrease in antihyperglycemic medication adherence after prescription opioid use, but explained that perhaps with better pain management, patients may have better health outcomes among patients with T2DM. Negative consequences of long-term opioid use cannot be ruled out and future studies with a longer follow-up period should be conducted to investigate whether long-term prescription opioid use negatively impacts antihyperglycemic medication adherence.

CHAPTER FOUR: MANUSCRIPT 2

IMPACT OF LONG-TERM OPIOID MEDICATION USE ON SUBSEQUENT TYPE 2 DIABETES MELLITUS RELATED HOSPITALIZATIONS

4.1 Abstract

Introduction: Patients' adherence to antihyperglycemic medication is an essential component in achieving adequate glycemic control. Non-adherence to antihyperglycemic medication can lead to macro vascular and micro vascular complication among patients with type 2 diabetes mellitus (T2DM). According to the SAMSHA opioid use guideline, prescription opioid use can potentially have a negative impact on chronic asymptomatic medication therapy. Thus, antihyperglycemic medication adherence may decrease and subsequently lead to T2DM related hospitalizations.

Methods: This study was a retrospective cohort analysis that utilized 2003-2004 US MarketScan® (Truven Health Analytics, Ann Arbor, MI, USA) commercial health insurance claims databases. Adults aged 18 years and older with T2DM who were prescribed prescription opioids were included. Adherence to antihyperglycemic medications was calculated among long-term (≥ 90 days) opioid users and short-term (< 90 days) opioid users. Patients with prior hospitalization before the index date were excluded. Adherence was measured using proportion of days covered (PDC), with PDC ≥0.80 considered adherent. Risk of subsequent T2DM related hospitalizations was estimated using a cox proportional hazard regression model by comparing long-term and short-term users of prescription opioids.

Results: There were 22,212 patients in the study, out of which 7,462 (33.66%) were long-term opioid users and 14,736 (66.34%) were short-term opioid users. During the 6-month follow-up, risk of T2DM related hospitalization was lower among long-term opioid users in 150 days or less during follow-up (HR = 0.73, 95% CI = 0.69-0.78) as compared to short-term prescription opioid

users. Whereas risk of T2DM related hospitalization was more among patients with long-term prescription opioid use greater than 150 days during the follow-up (HR = 1.25, 95% CI = 0.69-2.28) as compared to short-term opioid users. Follow up antihyperglycemic adherence (HR = 1.44, 95% CI = 1.25-1.64) was a significant predictor of T2DM related hospitalization when assessed as a mediator.

Conclusion: Patients who were concomitantly prescribed long-term prescription opioids and antihyperglycemic medications were at a lower risk of T2DM related hospitalizations as compared to patients who were prescribed short-term prescription opioids. Use of prescription opioids over a longer duration did not negatively impact T2DM related hospitalizations when prescribed concomitantly.

4.2 Background

Diabetes Mellitus (DM) is a chronic, progressive disorder characterized by hyperglycemia, which affects 9.3% of the total population of the U.S (W. C. Cho et al., 2006; Control & Prevention, 2014b). Approximately 1.4 million cases of DM are diagnosed in the US every year (Control & Prevention, 2014a). Of patients diagnosed with DM, 90% - 95% patients suffer from T2DM (Richardson & Pollack, 2005). T2DM management is also associated with a high economic burden. Furthermore, T2DM is associated with a significant decline in quality of life (Dall et al., 2010). A study by Condliffe et al. reported that in the year 2007, annual direct costs for T2DM management was $11,917 per person (Condliffe, Link, Parasuraman, & Pollack, 2013). Due to the progressive nature of the disorder, T2DM when not adequately treated can lead to macro vascular and micro vascular complications such neuropathy and nephropathy (Cade, 2008).

The progression towards macro vascular and micro vascular complications due to uncontrolled diabetes can prevented by maintaining adequate glycemic levels by using appropriate pharmacotherapy for T2DM management. Maintaining adherence to antihyperglycemic medications is thus a key factor in the proper management of T2DM. Non-adherence to antihyperglycemic medications leads to higher glycosylated hemoglobin, higher blood pressure and higher LDL cholesterol levels, all of which lead to micro vascular and macro vascular complications, which result in rapid progression of disease and an increased risk of cardiovascular disorders (Wabe, Angamo, & Hussein, 2011). However, despite these facts, adherence to oral antihyperglycemic medications has been found to be suboptimal among patients with T2DM. A study by Kirkman et al. reviewed the literature on antihyperglycemic medication adherence rates and found that adherence rates for oral antihyperglycemic agents ranged from 36% to 93% (Kirkman et al., 2015). Factors negatively affecting antihyperglycemic medication adherence lead

to poor T2DM management. Subpar antihyperglycemic medication adherence eventually results in T2DM related complications and poor patient outcomes characterized by increased hospitalizations related to T2DM (Lau & Nau, 2004).

Pain is an uncomfortable sensation in the body that suggests something underlying the pain is amiss. Chronic pain is often a comorbid condition that is troublesome for patients with T2DM given its associated physical disability and mental distress. Patients with T2DM often suffer from pain due to other comorbidities like arthritis and low back pain. A study by Sudore et al. reported that among patients with T2DM, 41.8% and 39.7% reported suffering from acute and chronic pain respectively (R. L. Sudore et al., 2012). Non-chronic pain among patients with T2DM is often caused by diabetic neuropathy. The presence of chronic pain among patients T2DM can influence patients T2DM care management (Sarah L. Krein, Michele Heisler, John D. Piette, Fatima Makki, & Eve A. Kerr, 2005).

The use of pharmacotherapy to alleviate pain is an important component of chronic pain management. Pharmacotherapy based management for chronic pain includes NSAIDs, opioid analgesics, antidepressants and anticonvulsants (American Diabetes Association, 2015). Prescription opioids have been regarded as the most effective medication for management of pain. Prescription opioid use in the management of chronic pain is considered a standard of care in the US. A dramatic increase in use of prescription opioids for chronic pain management has also occurred over the last two decades (Laxmaiah Manchikanti, 2012). The existing literature on long-term opioid use does not support the use of prescription opioids over long-term for chronic pain management due to concerns of negative consequences (e.g., abuse) (Kalso, Edwards, Moore, & McQuay, 2004). In addition, there is growing body evidence indicating increased rates of the

harmful effects associated with high prevalence of prescription opioid use, including accidental overdose, abuse, addiction, and diversion (Katz et al., 2013).

The Substance Abuse and Mental Health Services Administration (SAMHSA) guideline on chronic opioid use states that patients with long-term opioid use are more likely to demonstrate aberrant drug-related behaviors (ADRBs), which may negatively affect their adherence to other prescribed treatments (Substance Abuse and Mental Health Services Administration, 2012). Patients with ADRBs often demonstrate behaviors that are indicative of substance misuse, overuse, abuse, or addiction. Patients with ADRBs are also more likely to be interested in their prescription opioids than in their other chronic asymptomatic medications (e.g., antihypertensive) when prescribed concomitantly (Substance Abuse and Mental Health Services Administration, 2012). Patients with T2DM often suffer with chronic pain or cough which are often treated with prescription opioids. According to SAMHSA guidelines on opioids, the continuous use of prescription opioids over a long duration of time can lead to ADRBs, which can affect antihyperglycemic medication adherence among patients with T2DM patients.

Non-adherence to antihyperglycemic medication is associated with an increased risk of hospitalizations due to diabetes and cardiovascular complications (Sokol, McGuigan, Verbrugge, & Epstein, 2005). At least one study has shown that patients with adherence rates greater than 80% were significantly less likely to be hospitalized as compared with patients who had adherence less than 80% (Brown & Bussell, 2011). Even with the presence of existing evidence regarding antihyperglycemic medication adherence and subsequent hospitalization risk, there is limited research which has explored diabetes related outcomes (e.g., hospitalizations) when patients are prescribed prescription opioids (Lau & Nau, 2004). Therefore, the objective of this study was to evaluate the relationship between oral antihyperglycemic medication adherence and subsequent

risk of T2DM related hospitalization among patients, who were prescribed long-term prescription opioids as compared to patients who were prescribed short-term prescription opioids.

4.3 Methods

Data Source

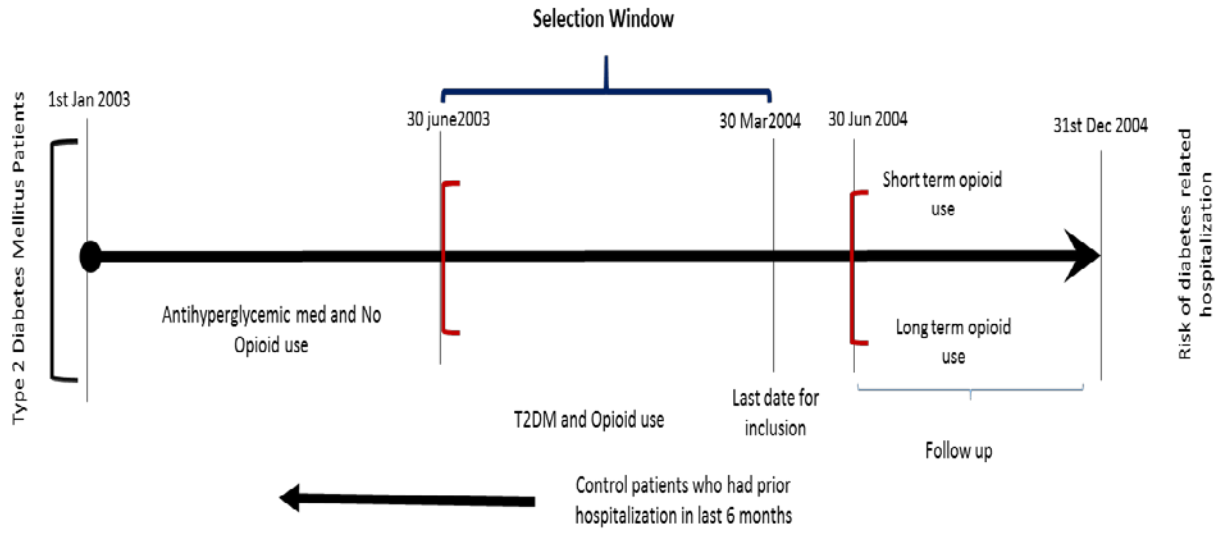
Administrative claims data from the Truven Health MarketScan® (Truven Health Analytics, Ann Arbor, MI, USA) was used to address the study objective. MarketScan® data is collected from employers, health plans, and state Medicaid agencies. This study was conducted using 2003-2004 MarketScan® Commercial Claims and Encounters Database. The database contains information about enrollees and their dependents, which were covered through employer sponsered healthpans.

4.4 Sample and Study Design

According to Figure 4.1, a retrospective study was designed to analyze the association between concomitant antihyperglycemic and prescription opioid use and its effect on T2DM related hospitalization risk while controlling for antihyperglycemic medication adherence. Patients aged 18 and older were included in the study cohort. Patients were required to be continuously enrolled for the study duration and have at least one T2DM diagnosis claim ([ICD-9-CM] 250.x0, 250.x2) in the baseline and follow-up duration. Also, these patients needed to have at least one outpatient pharmacy claim with a National Drug Code (NDC) for an antihyperglycemic medication (e.g., sulfonylureas, biguanide). Patients with any prescription opioid history or diabetes related hospitalizations were excluded. Patients identified in the selection window were

classified into long-term users of prescription opioids (≥ 90 days) and short-term users of prescription opioids (< 90 days) based on their 90-day persistence to opioid therapy. Once classified as long-term and short-term users of prescription opioids, risk of diabetes related hospitalization were compared taking into account their follow-up antihyperglycemic medication adherence. Antihyperglycemic adherence was measured over 6 months from the day the patient was classified as a long-term or short-term user of prescription opioids.

Figure 4.1 Study design to estimate T2DM related hospitalizations among patients prescribed prescription opioids



Outcome Variable

The objective of this study was to measure T2DM related hospitalization risk among patients with T2DM who were prescribed concomitantly an antihyperglycemic medication and prescription opioid. For each patient, the study identified T2DM related hospital admission during the follow-up period based on Table 4.1.

Table 4.1 ICD 9 – CM codes for T2DM related hospitalizations

Type of diabetes-related hospitalizations	**ICD-9 codes**
Uncontrolled T2DM	250.02
Septicemia or bacteremia	038.xx, 790.7
Pneumonia	480-6
Kidney infections, cystitis, urinary tract infection	590, 595, 599.0x
Cellulitis	680-682, 686
Electrolyte imbalance	276.xx
Diabetes retinopathy	250.5x, 361.xx, 362.0x, 362.1, 362.8x, 379.23, 369.xx
Diabetic nephropathy	250.4x, 585.xx, 593.9
Diabetic neuropathy	250.6x, 356.9, 357.2x
Ischemic heart disease	410-414,
Stroke	433-434
Diabetes peripheral circulatory disorders	250.7x, 440.2x, 707.1x, 785.4x

ICD 9 -CM - The International Classification of Diseases, Ninth Revision, Clinical Modification

Independent Variable

The primary independent variable of interest was duration of opioid therapy. Demographic and clinical variables were measured and controlled for potential confounding in the multivariable models. Demographic variables included were gender, age, geographic region, presence of capitated services, and insurance plan type. Non-diabetes related clinical characteristics were measured during the baseline period, and it was captured using the adapted Elixhauser comorbidity index, and diabetes-related clinical characteristics were measured using the adapted diabetes complications severity index (aDCSI). The adapted Elixhauser comorbidity index is used to calculate and predict in-hospital mortality. Whereas, the aDCSI is a DM specific severity scale used in predicting mortality and hospitalizations. The aDCSI is a modified version of the diabetes complications severity index, which is calculated with lab data (e.g., HbA1c). The aDCSI estimates diabetes severity using claims data are similar to DCSI diabetes severity estimates. The influence of antihyperglycemic adherence as a mediator on the hospitalization risk was evaluated by using two separate regression models, one with antihyperglycemic medication and the other without antihyperglycemic medication adherence being considered. Antihyperglycemic medication adherence was measured as the proportion of days covered (PDC), calculated by taking the number of days a patient had the T2DM medication while taking opioid medications on hand during the 180 days' follow-up divided by the follow-up time. Patients with PDC $\geq$ .80 were considered adherent to their prescribed antihyperglycemic medication.

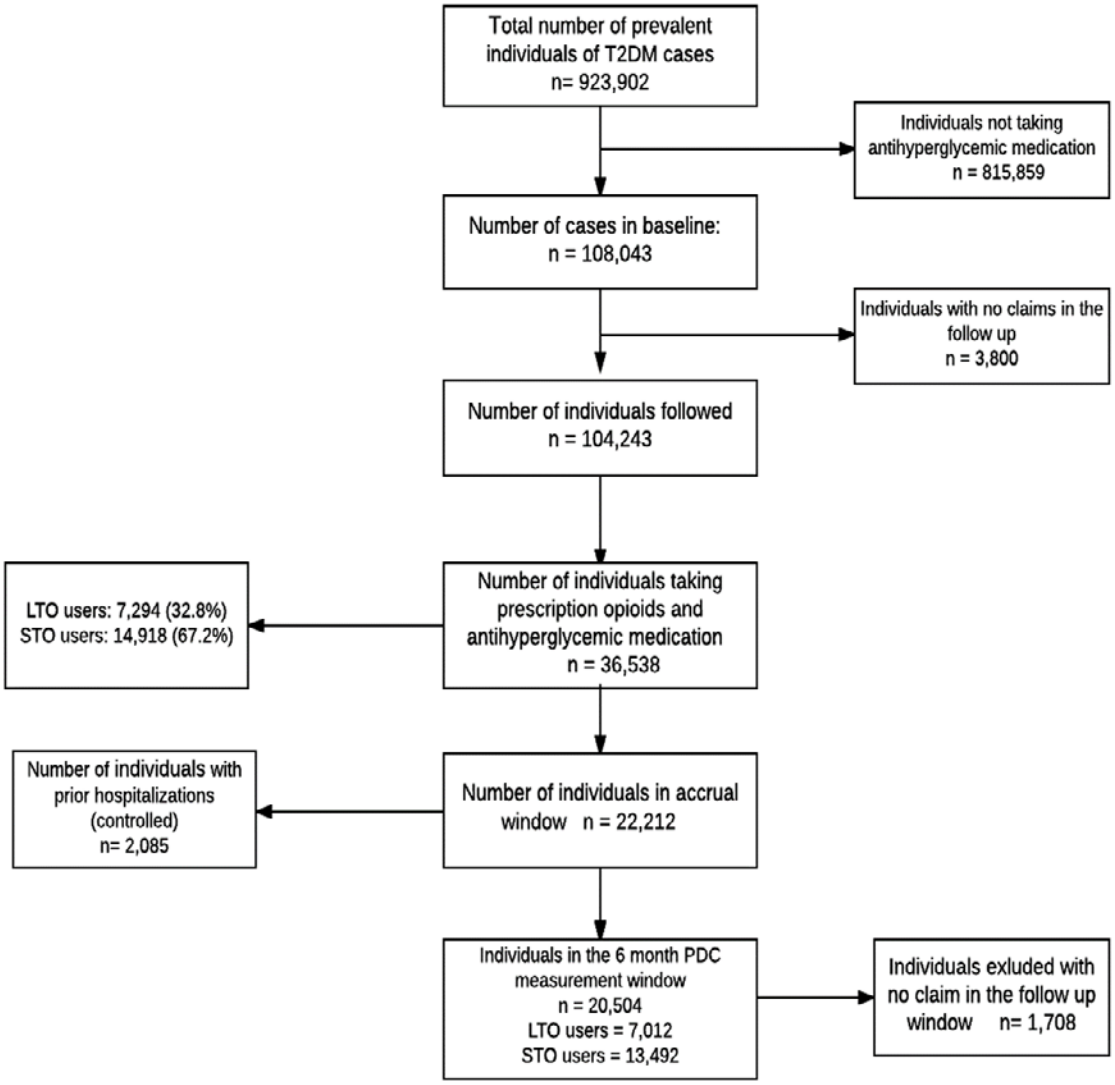
$$\text{PDC} = \frac{Total\ days\ antihyperglycemic\ medication\ available}{Days\ in\ follow{-}up\ period}$$

4.5 Statistical Analysis

For descriptive statistics, frequencies were measured for all study variables in both long-term and short-term opioid users. Cox proportional hazard regression models were fit to compare the subsequent T2DM related hospitalization risk among patients prescribed long-term prescription opioids versus patients prescribed short-term prescription opioids concomitantly along with their antihyperglycemic medications. Models controlled for the following variables: age, sex, region, insurance plan type, capitated payment and baseline diabetes adherence. Additionally, non-diabetes severity was controlled for by the adapted Elixhauser comorbidity index. Diabetes severity was controlled using the adapted diabetes complications severity index (aDCSI) score. A sensitivity analysis was conducted by defining the long-term prescription opioid use as greater than 60 days, with a maximum discontinuation of 5 days. Another sensitivity analysis was conducted among patients who were adherent to antihyperglycemic medication in the baseline duration (PDC $\geq$ 0.80). An apriori alpha of 0.05 was used to determine statistical significance. Analyses were conducted with SAS version 9.3 (SAS Institute Inc. Cary, NC, USA).

4.6 Patient Attrition Flowchart

Figure 4.2 Patient attrition flow chart



LTO - Long term opioid
STO - Short term opioid
PDC - Proportion of days covered

4.7 Results

Demographic Characteristics

Table 4.2 shows that there were 22,212 patients, out of which 7,476 (33.66%) were long-term opioid users and 14,736 (66.34%) were short-term opioid users. The mean age for patients with long-term opioid use was 55.82 ± 7.87 years and mean age for patients with short-term opioid usage was 53.13±6.52 years. The majority of long-term opioid users were males (53.04%) whereas most short-term opioid users were females (52.69%). Mean non-diabetes severity reported through the elixhauser index was 0.12 ± 1.10 for long-term opioid users, and it was 0.13 ± 1.06 for short-term users. Mean diabetes severity was 0.08 ± 0.37 for long-term opioid users and 0.08 ± 0.32 for short-term opioid users. The majority of patients in both groups were on non-capitated plans.

Table 4.2 Frequency and distribution of patient demographics

	Long-term opioid users		Short-term opioid users		P-Value
	N = 7,476		N = 14,736		
	Mean	SD	Mean	SD	
Age, years	55.82	7.87	53.13	6.52	<0.0001
Clinical characteristics					
aElixhauser index[a]	0.12	1.10	0.13	1.06	<0.0001
aDCSI[b]	0.08	0.37	0.08	0.32	<0.001
	N	%	N	%	
Gender					
Male	3,965	53.04	6,971	47.31	<0.0001
Female	3,511	46.96	7,765	52.69	<0.0001
Region					
Northeast	581	7.77	673	4.57	<0.0001
North Central	2,650	35.45	4,354	29.55	<0.0001
South	2,579	34.50	7,098	48.17	<0.0001
West	1,666	22.28	2,519	17.72	<0.0001
Insurance plan type					
Basic and comprehensive plans	1,904	25.47	2,567	17.42	<0.0001
Capitated plan	2,629	35.17	4,886	33.14	<0.0001
Non-capitated plan	2,916	39.00	7,246	49.17	<0.0001
CDHP and HDHP[c]	27	0.36	40	0.27	<0.0001
Presence of Capitated Payment					
Capitated	11,77	15.74	1,489	10.12	<0.0001
Non-capitated	6,299	84.26	13,230	89.88	<0.0001

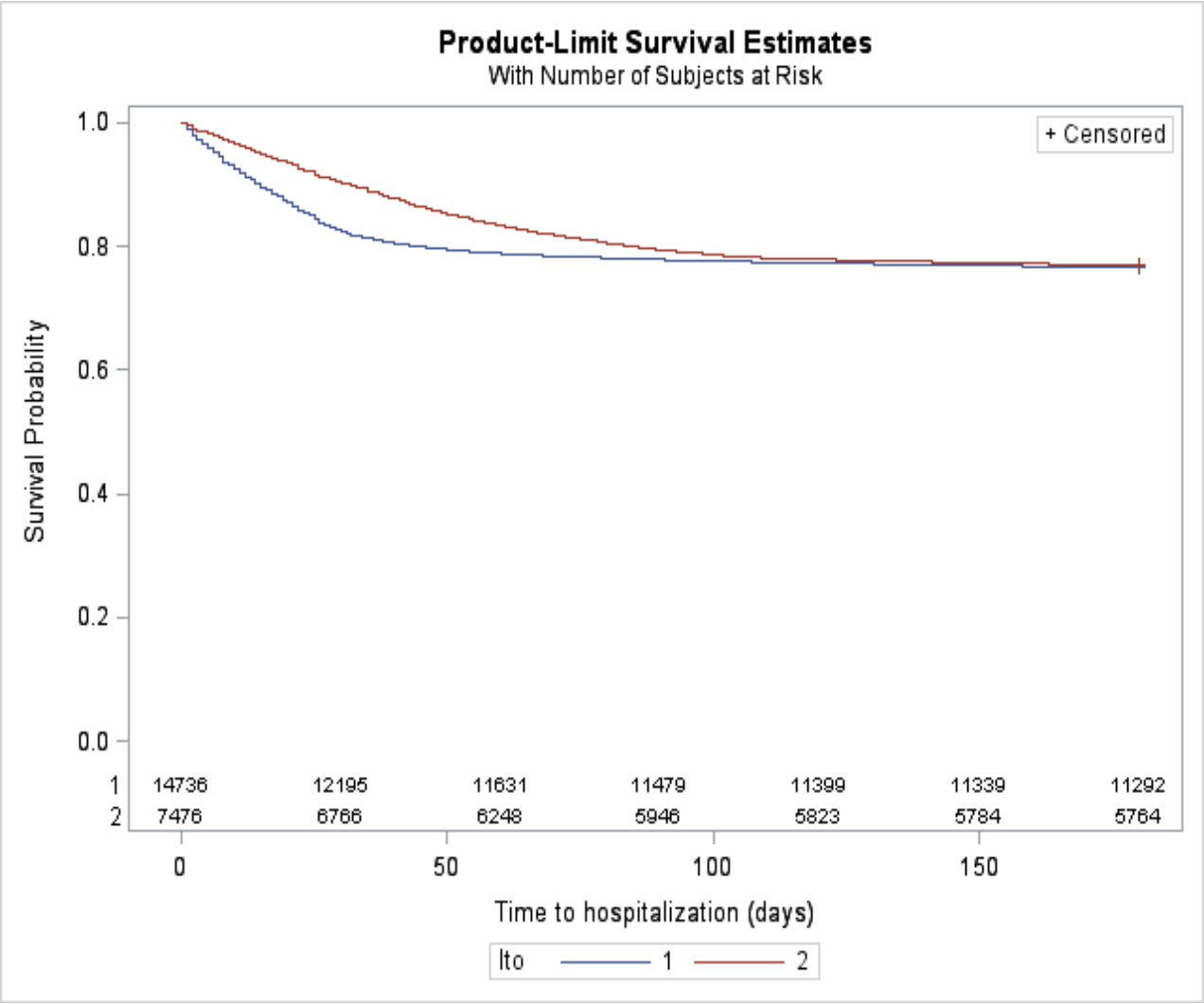
[a] Adapted Elixhauser Index
[b] Adapted diabetes severity comorbidity index
[c] Consumer-Driven Health Plan/High Deductible Health plan

Multivariable Cox Proportional Hazard Regression Analysis

Extended cox proportional hazard model was fit to determine the subsequent risk of T2DM related hospitalization among patients with T2DM who were prescribed antihyperglycemic medications and prescription opioids concomitantly. Two separate models were executed to measure the subsequent T2DM medication, with and without the mediation effect of follow up antihyperglycemic adherence.

Extended Cox proportional hazard analysis to estimate T2DM related hospitalizations without follow up antihyperglycemic adherence

Figure 4.3 Kaplan Meier curve to estimate T2DM related hospitalizations without follow up antihyperglycemic adherence



Findings from Table 4.3 show that risk of T2DM related hospitalization was less among long-term opioid users with 150 days or less of follow-up (HR = 0.80, 95% CI = 0.75-0.85) as compared to short-term opioid users. T2DM related hospitalization risk among long-term opioid users in greater than 150 days of follow-up (HR = 0.88, 95% CI = 0.52-1.49) as compared to short-term opioid users. Females (HR = 1.02, 95% CI = 0.97-1.08) were more likely to have T2DM related hospitalizations as compared to males. Patients in the age group of 31to 45 years (HR = 1.46, 95% CI = 1.07- 1.98), 46 to 60 years (HR = 1.52, 95% CI = 1.13 – 2.05) and patients above 60 years (HR = 1.52, 95% CI = 1.12 – 2.05) have higher risk of T2DM related hospitalizations as compared to patients in the age group of 18 to 30 years. Hospitalization risk increase significantly among patients with prior T2DM related hospitalization.

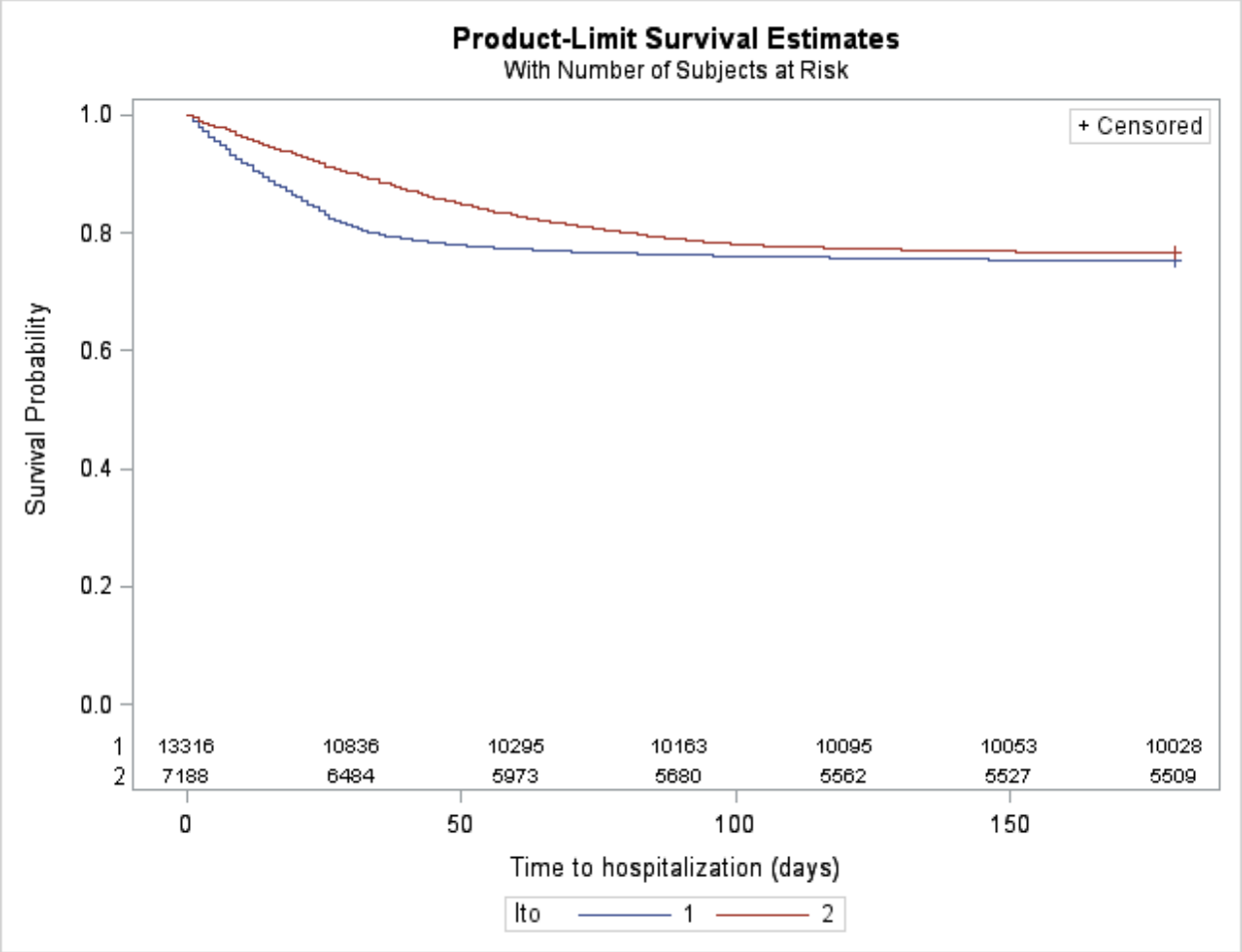
Table 4.3 Cox proportional hazard regression to study predictors of T2DM related hospitalizations without follow up antihyperglycemic adherence

Analysis of Maximum Likelihood Estimates					
Parameter	Parameter Estimate	Hazard Ratio	95% Confidence Limits		P Value
Opioid use (Ref = Short-term opioid use)					
Long-term opioid use (less than equal to 150 days)	-0.22	0.80	0.75	0.85	<.0001
Long-term opioid use (greater than 150 and less than equal to 180 days)	-0.13	0.88	0.52	1.49	0.63
Gender (Ref = Male)					
Female	0.02	1.02	0.97	1.08	0.40
Region (Ref = Northeast)					
North central	0.03	1.03	0.91	1.17	0.67
South	0.18	1.20	1.06	1.36	0.003
West	0.12	1.13	0.97	1.32	0.12
Age Category (Ref = 18 – 30 years)					
31- 45 years	0.38	1.46	1.07	1.98	0.02
46- 60 years	0.42	1.52	1.13	2.05	0.01
Greater than 60 years	0.42	1.52	1.12	2.05	0.01
Health Plan Type (Ref = Basic and comprehensive plans)					
Non capitated plan	0.06	1.06	0.97	1.16	0.23
Capitated plans	0.07	1.07	0.99	1.16	0.09
CDHP and HDHP[a]	-0.24	0.79	0.44	1.43	0.44
Non diabetes severity index					
aElixhauser Index[b]	-0.03	0.97	0.96	0.99	0.001
Diabetes severity Index					
aDCSI[c]	0.03	1.03	0.97	1.09	0.34
Prior hospitalization history					
Prior hospitalization	2.56	12.90	11.98	13.90	<.0001
Baseline antihyperglycemic adherence					
Baseline antihyperglycemic adherence	0.33	1.40	1.25	1.56	<.0001
Capitated service (Ref = No)					
Yes	-0.21	0.81	0.70	0.93	0.00

[a] Consumer-Driven Health Plan and High Deductible Health plan
[b] adapted Elixhauser Index
[c] Adapted diabetes severity comorbidity index

Extended Cox proportional hazard analysis to estimate T2DM related hospitalizations with follow up antihyperglycemic adherence

Figure 4.4 Kaplan Meier curve to estimate T2DM related hospitalizations with follow up antihyperglycemic adherence



Findings from Table 4.4 show that risk of T2DM related hospitalization was lower among patients with long-term opioid use with 150 days or less of follow-up (HR = 0.73, 95% CI = 0.69-0.78) as compared to short-term users. Whereas, among patients with long-term opioid use greater than 150 days (HR = 1.25, 95% CI = 0.69-2.28), risk of T2DM related hospitalizations increased as compared to short-term opioid users however, it was not significant. Females (HR = 1.02, 95% CI = 0.97-1.08) were more likely to have T2DM related hospitalizations as compared to males. Patients in age group of 31 to 45 years (HR = 1.27, 95% CI = 0.91- 1.78), 46 to 60 years (HR = 1.27, 95% CI = 0.92 – 1.76) and patients above 60 years (HR = 1.24, 95% CI = 0.89 – 1.72) had higher risk of T2DM related hospitalizations as compared to patients in age group of 18 to 30 years. Hospitalization risk increased significantly among patients with prior T2DM related hospitalization. Follow up antihyperglycemic adherence (HR = 1.44, 95% CI = 1.25 – 1.64) was a significant predictor of T2DM related hospitalization.

Table 4.4 Cox proportional hazard regression to study predictors of T2DM related hospitalizations with follow up antihyperglycemic adherence as a mediator

Analysis of Maximum Likelihood Estimates					
Parameter	Parameter Estimate	Hazard Ratio	95% Confidence Limits		P Value
Opioid use (Ref = Short-term opioid use)					
Long-term opioid use (less than equal to 150 days)	-0.32	0.73	0.69	0.78	<.01
Long-term opioid use (greater than 150 and less than equal to 180 days)	0.22	1.25	0.69	2.28	0.47
Gender (Ref = Male)					
Female	0.02	1.02	0.97	1.08	0.45
Region (Ref = Northeast)					
North central	-0.01	0.99	0.87	1.13	0.86
South	0.15	1.17	1.03	1.32	0.02
West	0.09	1.09	0.93	1.28	0.27
Age Category (Ref = 18 – 30 years)					
31- 45 years	0.24	1.27	0.91	1.78	0.16
46- 60 years	0.24	1.27	0.92	1.76	0.15
Greater than 60 years	0.21	1.24	0.89	1.72	0.21
Health Plan Type (Ref = Basic and comprehensive plans)					
Non capitated plan	0.06	1.06	0.97	1.17	0.18
Capitated plans	0.08	1.09	1.00	1.18	0.04
CDHP and HDHP[a]	-0.20	0.82	0.45	1.49	0.52
Non diabetes severity index					
aElixhauser Index[b]	-0.01	0.99	0.97	1.01	0.26
Diabetes severity Index					
aDCSI[c]	0.03	1.03	0.97	1.09	0.34
Prior hospitalization history					
Prior hospitalization	2.56	12.90	11.98	13.90	<.01
Baseline antihyperglycemic adherence					
Baseline antihyperglycemic adherence	0.14	1.16	1.02	1.31	0.02
Capitated service (Ref = No)					
Yes	-0.21	0.81	0.70	0.94	0. 04
Follow-up antihyperglycemic adherence					
Follow up antihyperglycemic adherence	0.36	1.44	1.25	1.64	<.01

[a] Consumer-Driven Health Plan and High Deductible Health plan
[b] adapted Elixhauser Index
[c] Adapted diabetes severity comorbidity index

4.8 Discussion

Prescription opioids are considered the most effective medication class for the management of chronic pain. However, there is limited evidence to support long-term use of opioids for pain management, due to concerns related regarding negative effects which includes ADRBs, which can potentially affect antihyperglycemic medication adherence. As seen in the results, without taking antihyperglycemic adherence into account, short-term users were more likely to have T2DM related hospitalizations. With follow-up antihyperglycemic adherence being accounted for, short- term users still were at a higher risk of T2DM related hospitalizations. The risk increased among long-term opioid users with the follow-up antihyperglycemic adherence, but it was not statistically significant. This reversal in pattern among long-term opioid users cannot conclude any negative impact of long-term opioid use on T2DM related hospitalizations. Future studies are needed in specific age populations to study any potential impact of ADRBs. In this study, lower hospitalization rates may be associated with patients, better managing their painful conditions, which leads to better management of their T2DM. Thus in turn leads to a lower risk for T2DM related hospitalizations.

There are a few limitations related to this study. Administrative claims data used for this study is collected for billing and reimbursement purposes by health care plans and may not be well suited for research purposes. Therefore, generating causal inferences from this study is not appropriate. Also, claims data often has data entry errors. Additionally, calculation for adherence (PDC) is based on days supplied and service dates, but it cannot be determined if the patient actually ingested the prescription medication. This database does not record cash payments, which is often the mode of payment among abusers who buy prescription opioids, instead of using their insurance. Also, the database used for this study is from 2003 -2004, thus limiting any new

medications approved after the study period. Finally, this data is limited to individuals on commercial health insurance plans; hence the findings from the study cannot be generalizable to the entire US population.

4.9 Conclusion

Short-term opioid use is associated with higher T2DM related hospitalization risks. To study the effects of long-term use and ADRBs among patients where antihyperglycemic and prescription opioids are concomitantly prescribed, future studies are needed with long-term follow-up among specific age categories where prescription opioid utilization rates are higher.

Executive Summary

Prescription opioids when prescribed concomitantly with antihyperglycemic medication adherence do not a demonstrate decrease in antihyperglycemic medication, and long-term opioid use is not associated with increased T2DM hospitalization risk.

Long-term use of prescription opioids and its negative consequences are well documented. Even though the current study was not able to establish any negative consequences regarding concomitant prescription opioid use on antihyperglycemic medication adherence, future studies are needed with a longer follow-up duration among patients with continuous opioid use of six months or greater.

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